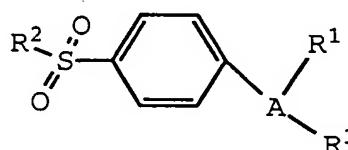


Seth
1
5
What is claimed is :

1. A combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a leukotriene B₄ receptor antagonist.

Sally
10
10 NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



I

15 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R¹ is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,

20 wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

25 wherein R² is methyl or amino; and

wherein R³ is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio,

30 alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, 35 aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl,

aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N-arylamino carbonyl, N-alkyl-N-arylamino carbonyl,
alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-
arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-
5 alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-
arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-
aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy,
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,
alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-
10 arylaminosulfonyl, arylsulfonyl, N-alkyl-N-
arylamino sulfonyl;
or a pharmaceutically-acceptable salt thereof.

3. The combination of Claim 2 wherein the
15 leukotriene B₄ receptor antagonist is selected from
Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo
Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo
TMK-688, Boehringer Ingelheim BI-RM-270, Lilly LY
213024, Lilly LY 264086, Lilly LY 292728, Ono ONO
20 LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-
Poulenc Rorer RP 66153, SmithKline Beecham SB-201146,
SmithKline Beecham SB-201993, Searle SC-53228, Sumitomo
SM 15178, American Home Products WAY 121006, Bayer Bay-
o-8276, calcitriol, Warner-Lambert CI-987, Merck and
25 Co. L-651392, Lilly LY 210073, Lilly LY 223982, Lilly
LY 233569, Lilly LY-255283, Merck and Co. MK-591, Merck
and CO. MK-886, Ono ONO-LB-448, Purdue Frederick PF-
5901, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer
RP 66364, Rhone-Poulenc Rorer RP 69698, Searle SC-
30 41930, Searle SC-50505, Searle SC-51146, SmithKline
Beecham SK&F-104493, and Teijin TEI-1338.

4. The combination of Claim 3 wherein the
leukotriene B₄ receptor antagonist is selected from
35 Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo
Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, Terumo
TMK-688, Boehringer Ingelheim BI-RM-270, Lilly LY

213024, Lilly LY 264086, Lilly LY 292728, Ono ONO LB457,
Pfizer 105696, Perdue Frederick PF 10042, Rhone-Poulenc
Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline
Beecham SB-201993, Searle SC-53228, Sumitomo SM 15178,
and American Home Products WAY 121006.

5. The combination of Claim 4 wherein the leukotriene B₄ receptor antagonist is selected from Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-615, Lilly LY-293111, Ono ONO-4057, and Terumo TMK-688.

6. The combination of Claim 2 wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R¹ is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from lower-alkyl, lower-haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R² is methyl or amino; and wherein R³ is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, lower hydroxylalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminoalkyl, lower alkylaminoalkyl, phenoxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

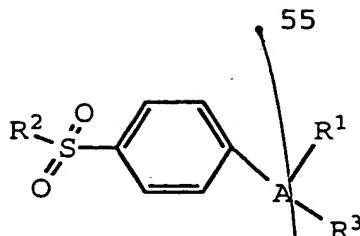
7. The combination of Claim 6 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, 5 imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R¹ is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a 10 substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, carboxyl, methoxycarbonyl, ethoxycarbonyl, hydroxymethyl, 15 trifluoromethoxy, hydroxyl, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, methoxymethyl, methylsulfinyl, fluoro, chloro, bromo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and 20 methylthio; wherein R² is methyl or amino; and wherein R³ is a radical selected from hydrido, oxo, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, carboxypropyl, carboxymethyl, carboxyethyl, cyanomethyl, fluoro, chloro, bromo, methyl, ethyl, 25 isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl, 30 oxazolyl, furyl, pyrazinyl, hydroxymethyl, hydroxylpropyl, benzyl, formyl, phenylcarbonyl, methoxymethyl, furylmethoxy, aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-dimethylaminomethyl, N-methyl-N-ethylaminomethyl, 35

benzyloxy, and phenoxy; or a pharmaceutically-acceptable salt thereof.

8. The combination of Claim 7 selected from
5 compounds and their pharmaceutically-acceptable salts,
of the group consisting of

- 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-
1-yl]benzenesulfonamide;
- 10 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-
yl]benzenesulfonamide;
- 15 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-
pyrazol-1-yl]benzenesulfonamide;
- 20 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-
imidazol-2-yl]pyridine;
- 25 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-
trifluoromethyl-1H-imidazol-2-yl]pyridine;
- 30 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-
imidazol-1-yl]benzenesulfonamide;
- 35 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 40 4-[5-hydroxymethyl-3-phenylisoxazol-4-
yl]benzenesulfonamide;
- 45 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-
oxazolyl]benzenesulfonamide;
- 50 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and
- 55 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl)-4-
oxazolyl]benzenesulfonamide.

60 *SuJ* 9. A pharmaceutical composition comprising a
therapeutically-effective amount of a leukotriene B₄
receptor antagonist and a cyclooxygenase-2 inhibitor
selected from Taisho NS-398, meloxicam, floculide, Merck
MK-966, Merck L-752,860 and compounds of Formula I



I

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

5 wherein R¹ is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

10 wherein R² is methyl or amino; and

15 wherein R³ is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,

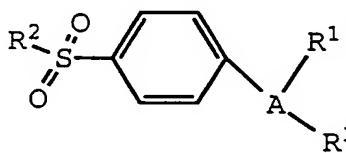
20 25 N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amido, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-
30 aralkylaminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

M

or a pharmaceutically-acceptable salt thereof.

10. A method of treating inflammation or an inflammation-associated disorder in a subject, said

- 5 method comprising co-administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a leukotriene B₄ receptor antagonist and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



I

15 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R¹ is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,

- 20 wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfanyl, halo, alkoxy and alkylthio;

wherein R² is methyl or amino; and

wherein R³ is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloloxy, alkyloxy, alkylthio,

- 30 alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,

aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl,
aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl,
alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-
5 arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-
alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-
arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-
aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy,
aralkoxy, arylthio, aralkylthio, alkylsulfinyl,
10 alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-
arylaminosulfonyl, arylsulfonyl, N-alkyl-N-
arylaminosulfonyl;
or a pharmaceutically acceptable salt thereof.

15 11. The method of Claim 10 wherein said leukotriene B₄
receptor antagonist and said cyclooxygenase-2 inhibitor are
administered in a sequential manner.

20 12. The method of Claim 10 wherein said leukotriene B₄
receptor antagonist and said cyclooxygenase-2 inhibitor are
administered in a substantially simultaneous manner.

25 13. The method of Claim 10 wherein the leukotriene
B₄ receptor antagonist is selected from Bayer Bay-x-
1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-
615, Lilly LY-293111, Ono ONO-4057, Terumo TMK-688,
Boehringer Ingelheim BI-RM-270, Lilly LY 213024, Lilly
LY 264086, Lilly LY 292728, Ono ONO LB457, Pfizer
105696, Perdue Frederick PF 10042, Rhone-Poulenc Rorer
30 RP 66153, SmithKline Beecham SB-201146, SmithKline
Beecham SB-201993, Searle SC-53228, Sumitomo SM 15178,
and American Home Products WAY 121006.

35 14. The method of Claim 13 wherein the leukotriene
B₄ receptor antagonist is selected from Bayer Bay-x-
1005, Ciba-Geigy CGS-25019C, ebselen, Leo Denmark ETH-
615, Lilly LY-293111, Ono ONO-4057, and Terumo TMK-688.

15. The method of Claim 10 wherein A is selected from 5- or 6-member partially unsaturated heterocyclyl, 5- or 6-member unsaturated heterocyclyl, 9- or 10-member unsaturated condensed heterocyclyl, lower cycloalkenyl and phenyl; wherein R¹ is selected from 5- and 6-membered heterocyclyl, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio; wherein R² is methyl or amino; and wherein R³ is a radical selected from hydrido, oxo, cyano, carboxyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, halo, lower alkyl, lower alkyloxy, lower cycloalkyl, phenyl, lower haloalkyl, 5- or 6-membered heterocyclyl, lower hydroxylalkyl, lower aralkyl, acyl, phenylcarbonyl, lower alkoxyalkyl, 5- or 6-membered heteroaryloxy, aminocarbonyl, lower alkylaminocarbonyl, lower alkylamino, lower aminealkyl, lower alkylaminoalkyl, phenoxy, and lower aralkoxy; or a pharmaceutically-acceptable salt thereof.

16. The method of Claim 15 wherein A is selected from oxazolyl, isoxazolyl, thienyl, dihydrofuryl, furyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, isothiazolyl, benzofuryl, cyclopentenyl, cyclopentadienyl, phenyl, and pyridyl; wherein R¹ is selected from pyridyl optionally substituted at a substitutable position with one or more methyl radicals, and phenyl optionally substituted at a substitutable position with one or more radicals selected from methyl, ethyl, isopropyl, butyl, tert-

butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl,
difluoromethyl, trifluoromethyl, carboxyl,
methoxycarbonyl, ethoxycarbonyl, hydroxymethyl,
trifluoromethoxy, hydroxyl, amino, N-methylamino, N,N-
5 dimethylamino, N-ethylamino, N,N-dipropylamino, N-
butylamino, N-methyl-N-ethylamino, phenylamino,
methoxymethyl, methylsulfinyl, fluoro, chloro, bromo,
methoxy, ethoxy, propoxy, n-butoxy, pentoxy, and
methylthio; wherein R² is methyl or amino; and wherein
10 R³ is a radical selected from hydrido, oxo, cyano,
carboxyl, methoxycarbonyl, ethoxycarbonyl,
carboxypropyl, carboxymethyl, carboxyethyl,
cyanomethyl, fluoro, chloro, bromo, methyl, ethyl,
isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl,
15 difluoromethyl, trifluoromethyl, pentafluoroethyl,
heptafluoropropyl, difluoroethyl, difluoropropyl,
methoxy, ethoxy, propoxy, n-butoxy, pentoxy,
cyclohexyl, phenyl, pyridyl, thienyl, thiazolyl,
oxazolyl, furyl, pyrazinyl, hydroxymethyl,
20 hydroxylpropyl, benzyl, formyl, phenylcarbonyl,
methoxymethyl, furylmethoxy, aminocarbonyl, N-
methylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-
dimethylamino, N-ethylamino, N,N-dipropylamino, N-
butylamino, N-methyl-N-ethylamino, aminomethyl, N,N-
25 dimethylaminomethyl, N-methyl-N-ethylaminomethyl,
benzyloxy, and phenoxy; or a pharmaceutically-
acceptable salt thereof.

17. The method of Claim 16 selected from compounds
30 and their pharmaceutically-acceptable salts, of the
group consisting of

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-
y1]benzenesulfonamide;
35 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-
y1]benzenesulfonamide;

60

4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

5 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

10 4-[5-hydroxyethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; and

15 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide.

18. The method of Claim 10 wherein the condition is inflammation.

20

19. The method of Claim 10 wherein the condition is an inflammation-associated disorder.

25 20. The method of Claim 19 wherein the inflammation-associated disorder is arthritis.

21. The method of Claim 10 wherein the subject is susceptible to inflammation.

30 22. The method of Claim 10 wherein the subject is susceptible to an inflammation-associated disorder.

23. The method of Claim 22 wherein the subject is susceptible to arthritis.